

WHAT IS CLAIMED:

1. A recombinant chimer hepatitis B core (HBc) protein molecule up to about 515 amino acid residues in length that

(a) contains an HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues,

(b) contains one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contains a sequence of at least 5 amino acid residues from HBc position 135 to the HBc C-terminus,

said chimer molecules (i) containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids on expression in a host cell, and said particles being more stable than are particles formed from an otherwise identical HBc chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue.

2. The recombinant HBC chimer protein molecule according to claim 1 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

3. The recombinant HBC chimer protein molecule according to claim 2 wherein said heterologous epitope is a B cell epitope.

4. The recombinant HBC chimer protein molecule according to claim 3 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBC.

5. The recombinant HBC chimer protein molecule according to claim 3 wherein said B cell epitope is peptide-bonded at a position in the HBC sequence between amino acid residues 76 and 85, and at least 5 residues of the HBC sequence of positions 76 through 85 are present.

6. The recombinant HBC chimer protein molecule according to claim 5 wherein the HBC sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

7. The recombinant HBC chimer protein molecule according to claim 2 further including a peptide-bonded heterologous T cell epitope.

8. The recombinant HBC chimer protein molecule according to claim 7 wherein said T cell

epitope is peptide-bonded to the C-terminal HBC amino acid residue.

9. The recombinant HBC chimer protein molecule according to claim 8 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBC chimer protein molecule.

10. The recombinant HBC chimer protein molecule according to claim 1 wherein said chimer contains the uninterrupted HBC amino acid residue sequence of position 1 through at least position 140, plus a cysteine residue at the C-terminus of the HBC chimer protein molecule.

11. The recombinant HBC chimer protein molecule according to claim 10 wherein said chimer contains the uninterrupted HBC amino acid residue sequence of position 1 through position 149.

12. The recombinant HBC chimer protein molecule according to claim 1 wherein said chimer contains a heterologous linker residue for a conjugated epitope.

13. The recombinant HBC chimer protein molecule according to claim 12 wherein said heterologous linker residue for a conjugated epitope is peptide-bonded at a position in the HBC sequence between amino acid residues 76 and 85, and at least 4 residues of the HBC sequence of positions 76 through 85 are present.

14. The recombinant HBc chimer protein molecule according to claim 13 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous linker residue for a conjugated epitope.

15. The recombinant HBc chimer protein molecule according to claim 14 that contains the HBc amino acid residue sequence of position 1 through at least position 140, plus a single cysteine residue at the C-terminus.

16. The recombinant HBc chimer protein molecule according to claim 15 wherein said chimer contains the HBc amino acid residue sequence of position 1 through position 149.

17. The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

18. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 135 to about 515 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBc and optionally includes a

heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBC residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBC residue 75 of Domain I in which (i) zero to all residues in a sequence of HBC positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBC and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBC at positions 76 to 85 is present free from heterologous residues, or (iii) one or more of residues 76 to 85 is absent;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) zero through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBC from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii),

said chimer self-assembling into particles on expression in a host cell, said particles being substantially free of binding to nucleic acids and more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-

terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer.

19. The recombinant HBc chimer protein molecule according to claim 18 that contains two heterologous epitopes.

20. The recombinant HBc chimer protein molecule according to claim 19 wherein said two heterologous epitopes are present in Domains I and II, II and IV or I and IV.

21. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope.

22. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a T cell epitope.

23. The recombinant HBc chimer protein molecule according to claim 19 wherein one of said two heterologous epitopes is a B cell epitope and the other is a T cell epitope.

24. The recombinant HBc chimer protein molecule according to claim 18 wherein said Domain I includes a heterologous epitope peptide-bonded to one of HBc residues 1-4.

25. The recombinant HBC chimer protein molecule according to claim 24 wherein said heterologous epitope of Domain II is a B cell epitope.

26. The recombinant HBC chimer protein molecule according to claim 25 wherein said sequence heterologous to HBC from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBC residues 140-149.

27. The recombinant HBC chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous epitope.

28. The recombinant HBC chimer protein molecule according to claim 27 wherein said heterologous epitope comprises up to about 245 amino acid residues.

29. The recombinant HBC chimer protein molecule according to claim 28 wherein said heterologous epitope is a B cell epitope.

30. The recombinant HBC chimer protein molecule according to claim 27 wherein said heterologous epitope contains 6 to about 50 amino acid residues.

31. The recombinant HBC chimer protein molecule according to claim 27 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

32. The recombinant HBc chimer protein molecule according to claim 27 wherein said Domain IV comprises 1 to about 5 cysteine residues within about 30 residues from the C-terminus of the chimer molecule.

33. The recombinant HBc chimer protein molecule according to claim 27 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

34. The recombinant HBc chimer protein molecule according to claim 18 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule.

35. The recombinant HBc chimer protein molecule according to claim 18 wherein said sequence heterologous to HBc from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBc residues 140-149.

36. The recombinant HBc chimer protein molecule according to claim 18 wherein said heterologous linker residue for a conjugated epitope or a heterologous epitope is a heterologous linker residue for a conjugated epitope.

37. The recombinant HBc chimer protein molecule according to claim 36 wherein said heterologous linker residue for a conjugated epitope

is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

38. The recombinant HBc chimer protein molecule according to claim 37 that contains a single cysteine residue at the C-terminus of the HBc chimer protein molecule.

39. The recombinant HBc chimer protein molecule according to claim 18 wherein said chimer contains the uninterrupted HBc amino acid residue sequence through at least position 140.

40. The recombinant HBc chimer protein molecule according to claim 39 wherein said uninterrupted HBc amino acid residue sequence includes residue 1.

41. The recombinant HBc chimer protein molecule according to claim 39 wherein said uninterrupted HBc amino acid residue sequence includes residue 149.

42. A recombinant hepatitis B virus core (HBc) protein chimer molecule with a length of about 175 to about 240 amino acid residues that contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBC residue 75 of Domain I in which at least 4 residues in a sequence of HBC positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBC and constitute a heterologous epitope;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) 5 through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) a cysteine residue [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBC from position 150 to the C-terminus,

said chimer self-assembling into particles on expression in a host cell that exhibit a ratio of absorbance at 280 nm to 260 nm of about 1.2 to about 1.6 and are more stable than are particles formed from an otherwise identical HBC chimer molecule that lacks said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBC sequence of the chimer.

43. The recombinant HBC chimer protein molecule according to claim 42 wherein said

heterologous epitope of Domain II is a B cell epitope.

44. The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 15 to about 50 amino acid residues.

45. The recombinant HBc chimer protein molecule according to claim 43 wherein said heterologous epitope contains 20 to about 30 amino acid residues.

46. The recombinant HBc chimer protein molecule according to claim 43 wherein the HBc sequence between amino acid residues 76 and 85 is present, but interrupted by said heterologous epitope.

47. The recombinant HBc chimer protein molecule according to claim 43 wherein said B cell epitope is an amino acid sequence present in a pathogen selected from the group consisting of *Streptococcus pneumonia*, *Cryptosporidium parvum*, HIV, foot-and-mouth disease virus, influenza virus, *Yersinia pestis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Porphyromonas gingivalis*, *Trypanosoma cruzi*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium berghi*, *Plasmodium yoelli*, *Streptococcus sobrinus*, *Shigella flexneri*, RSV, *Plasmodium Entamoeba histolytica*, *Schistosoma japonicum*, *Schistosoma mansoni*, bovine inhibin and ebola virus.

48. The recombinant HBC chimer protein molecule according to claim 43 wherein said sequence heterologous to HBC from position 150 to the C-terminus is a T cell epitope peptide-bonded to one of HBC residues 140-149.

49. The recombinant HBC chimer protein molecule according to claim 48 wherein said T cell epitope is from the organism against which a contemplated chimer is to be used as an immunogen.

50. The recombinant HBC chimer protein molecule according to claim 43 wherein said C-terminal cysteine residue is located within about five amino acid residues of the C-terminus of the chimer protein molecule.

51. An immunogenic particle comprised of recombinant hepatitis B core (HBC) chimeric protein molecules, said chimeric protein (i) displaying one or more immunogenic epitopes at the N-terminus, HBC immunogenic loop or C-terminus, or (ii) having a heterologous linker residue for a conjugated epitope in the HBC immunogenic loop, and containing a cysteine residue at or near the C-terminus, said particle being substantially free of nucleic acid binding and exhibiting enhanced stability relative to particles comprised of otherwise identical proteins that are free of said cysteine residue.

52. The immunogenic particle according to claim 51 that exhibits a 280/260 absorbance ratio of about 1.2 to about 1.7.

53. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the N-terminus.

54. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope at the C-terminus.

55. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays an immunogenic epitope in the immunogenic loop.

56. The immunogenic particle according to claim 1 whose recombinant HBc chimeric protein displays a B cell immunogenic epitope.

57. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays a T cell immunogenic epitope.

58. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein displays separate B cell and T cell immunogenic epitopes.

59. The immunogenic particle according to claim 51 whose recombinant HBc chimeric protein has a heterologous linker residue for a conjugated epitope in the HBc immunogenic loop.

60. The immunogenic particle according to claim 59 wherein said heterologous linker residue for a conjugated epitope is selected from the group

consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue.

61. The immunogenic particle according to claim 60 wherein said heterologous linker residue for a conjugated epitope is conjugated to a hapten.

62. The immunogenic particle according to claim 61 wherein said hapten is an oligosaccharide.

63. An immunogenic particle comprised of a plurality of recombinant chimeric hepatitis B core (HBc) protein molecules;

said recombinant chimeric HBc protein molecules having a length of up to about 515 amino acid residues that

(a) contain a HBc sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBc immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBc amino acid residues,

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contain a sequence of at least 6 amino acid residues from HBc position 135 to the HBc C-terminus,

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said chimer molecules containing no more than 10 percent conservatively substituted amino acid residues in the HBC sequence, and

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue, and having an amino acid residue sequence in which no more than about 20 percent of the amino acid residues are substituted in the HBC sequence of the chimer.

64. The immunogenic particle according to claim 63 that exhibits a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6.

65. The immunogenic particle according to claim 63 wherein the length of said recombinant chimeric HBC protein molecules is about 175 to about 240 amino acid residues.

66. The immunogenic particle according to claim 63 wherein said peptide-bonded heterologous epitope or a heterologous linker residue for a conjugated epitope is a heterologous epitope.

67. The immunogenic particle according to claim 66 wherein said heterologous epitope is a B cell epitope.

68. The immunogenic particle according to claim 63 wherein the length of said recombinant

chimeric HBC protein molecules is up to about 435 amino acid residues.

69. The immunogenic particle according to claim 63 that contains a second heterologous epitope peptide-bonded to one of amino acid residues 1-4 of HBC.

70. The immunogenic particle according to claim 68 wherein said B cell epitope is peptide-bonded at a position in the HBC sequence between amino acid residues 76 and 85, and at least 5 residues of the HBC sequence of positions 76 through 85 are present.

71. The immunogenic particle according to claim 70 wherein the HBC sequence between amino acid residues 76 and 85 is present, but interrupted by said B cell epitope.

72. The immunogenic particle according to claim 68 further including a peptide-bonded heterologous T cell epitope.

73. The immunogenic particle according to claim 72 wherein said T cell epitope is peptide-bonded to the C-terminal HBC amino acid residue.

74. The immunogenic particle according to claim 73 wherein said C-terminal cysteine residue(s) is present within five amino acid residues of the C-terminus of the HBC chimer protein molecule.

75. The immunogenic particle according to claim 63 wherein said recombinant chimeric HBC protein molecules have a length of about 135 to about 515 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBC and optionally includes a heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBC residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBC residue 75 of Domain I in which (i) zero to all of the residues in a sequence of HBC positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBC and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBC at positions 76 to 85 is present free from heterologous residues;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) zero through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, and (iii) zero to

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), said chimeric HBc protein having an amino acid residue sequence in which no more than about 10 percent of the amino acid residues are substituted in the HBc sequence.

76. The immunogenic particle according to claim 75 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.

77. The immunogenic particle according to claim 76 wherein said hapten is a B cell immunogen.

78. The immunogenic particle according to claim 63 wherein said recombinant chimeric HBc protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBc;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which at least 4 residues in a sequence of HBc positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues

that are heterologous to HBC and constitute a heterologous epitope;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) 5 through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to about five cysteine residues [C-terminal cysteine residue] within about 30 residues from the C-terminus of the chimera molecule, and (iii) zero to about 50 amino acid residues in a sequence heterologous to HBC from position 150 to the C-terminus,

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6, and said chimeric HBC protein having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBC sequence.

79. A vaccine or inoculum comprising an immunogenic effective amount of immunogenic particles dissolved or dispersed in a pharmaceutically acceptable diluent, wherein said immunogenic particles are comprised of a plurality of recombinant chimeric hepatitis B core (HBC) protein molecules in which said recombinant chimeric HBC protein molecules have a length of up to about 515 amino acid residues that

(a) contain a sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBC molecule that include a peptide-bonded

heterologous epitope or a heterologous linker residue for a conjugated epitope present in the HBC immunodominant loop, or a sequence of at least about 135 residues of the N-terminal 150 HBC amino acid residues,

(b) contain one to ten cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)],

(c) contain a sequence of at least 6 amino acid residues from HBC position 135 to the HBC C-terminus,

said chimer molecules containing no more than 20 percent conservatively substituted amino acid residues in the HBC sequence, and

said particles being substantially free of binding to nucleic acids, and being more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue.

80. The vaccine or inoculum according to claim 79 wherein said recombinant chimeric HBC protein molecules have a length of about 135 to about 515 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about 71 to about 100 amino acid residues whose sequence includes at least the sequence of the residues of position 5 through position 75 of HBC and optionally includes a

heterologous epitope containing up to about 30 amino acid residues peptide-bonded to one of HBC residues 1-4;

(b) Domain II comprises about 5 to about 250 amino acid residues peptide-bonded to HBC residue 75 of Domain I in which (i) at least 4 residues in a sequence of HBC positions 76 through 85 are present peptide-bonded to one to about 245 amino acid residues that are heterologous to HBC and constitute a heterologous epitope or a heterologous linker residue for a conjugated epitope or (ii) the sequence of HBC at positions 76 to 85 is present free from heterologous residues;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

d) Domain IV comprises (i) zero through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, (ii) one to ten cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimera molecule, and (iii) zero to about 100 amino acid residues in a sequence heterologous to HBC from position 150 to the C-terminus, with the proviso that Domain IV contain at least 6 amino acid residues including said one to ten cysteine residues of (ii), said recombinant chimeric HBC protein molecules having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBC sequence.

81. The vaccine or inoculum according to claim 80 that contains a heterologous linker residue for a conjugated epitope in Domain II and further includes a hapten linked to said heterologous linker residue.

82. The vaccine or inoculum according to claim 79 wherein said recombinant chimeric HBC protein molecules have a length of about 175 to about 240 amino acid residues and contain four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein

(a) Domain I comprises about the sequence of the residues of position 1 through position 75 of HBC;

(b) Domain II comprises about 5 to about 55 amino acid residues peptide-bonded to HBC residue 75 of Domain I in which at least 4 residues in a sequence of HBC positions 76 through 85 are present peptide-bonded to 6 to about 50 amino acid residues that are heterologous to HBC and constitute a heterologous epitope;

(c) Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II; and

(d) Domain IV comprises (i) 5 through fourteen residues of a HBC amino acid residue sequence from position 136 through 149 peptide-bonded to the residue of position 135 of Domain III, and (ii) zero to about 50 amino acid residues in a sequence heterologous to HBC from position 150 to the C-terminus,

said particles exhibiting a ratio of absorbance at 280 nm to 260 nm of about 1.4 to about 1.6.

83. The vaccine or inoculum according to claim 79 that is adapted for parenteral administration.

84. The vaccine or inoculum according to claim 79 that is adapted for mucosal immunization.

85. The vaccine or inoculum according to claim 79 wherein said recombinant chimeric HBC protein molecule particles are present in an attenuated strain of *S. typhi*, *S. typhimurium* or a *S. typhimurium-E. coli* hybrid.

86. The vaccine or inoculum according to claim 79 wherein said recombinant chimeric HBc protein molecule particles are present in plant tissue.

87. The vaccine or inoculum according to claim 79 that further includes an adjuvant.

88. The vaccine or inoculum according to claim 87 wherein said adjuvant is alum.

89. The vaccine or inoculum according to claim 87 wherein said adjuvant is a small molecule selected from the group consisting of a muramyl dipeptide, 7-substituted-8-oxo- or 8-sulfo-guanosine derivative, monophosphoryl lipid A, aluminum or calcium salts.

90. The vaccine or inoculum according to claim 87 wherein said adjuvant is an oil that is emulsified with said immunogenic particles and said pharmaceutically acceptable diluent.

91. The vaccine or inoculum according to claim 90 wherein said emulsion is an water-in-oil emulsion having a water phase and an oil phase.

92. The vaccine or inoculum according to claim 90 wherein said emulsion is an oil-in-water emulsion having a water phase and an oil phase.

93. The vaccine or inoculum according to claim 92 wherein the oil phase of said emulsion comprises squalene.

94. The vaccine or inoculum according to claim 92 wherein the oil phase of said emulsion comprises squalane.

95. The vaccine or inoculum according to claim 90 wherein the water and oil phases of said emulsion are emulsified by an emulsifying agent that is a sorbitan or mannide C<sub>12</sub>-C<sub>24</sub> fatty acid ester.

96. The vaccine or inoculum according to claim 95 wherein said emulsifying agent is a mannide C<sub>12</sub>-C<sub>24</sub> fatty acid ester.

97. The vaccine or inoculum according to claim 96 wherein said C<sub>12</sub>-C<sub>24</sub> fatty acid of said mannide C<sub>12</sub>-C<sub>24</sub> fatty acid ester is oleic acid.

98. A nucleic acid that encodes a recombinant HBC protein molecule according to claim 1, or a variant, analog or complement thereof.

99. A nucleic acid that encodes a recombinant HBC protein molecule according to claim 18, or a variant, analog or complement thereof.

100. A nucleic acid that encodes a recombinant HBC protein molecule according to claim 42, or a variant, analog or complement thereof.

101. A recombinant nucleic acid molecule that comprises a vector operatively linked to a nucleic acid segment defining a gene that encodes a recombinant HBC protein molecule according to claim 1, or a variant, analog or complement thereof, and a promoter suitable for driving the expression of the gene in a compatible host organism.

102. A recombinant nucleic acid molecule that comprises a vector operatively linked to a nucleic acid segment defining a gene that encodes a recombinant HBC protein molecule according to claim 18, or a variant, analog or complement thereof, and a promoter suitable for driving the expression of the gene in a compatible host organism.

103. A recombinant nucleic acid molecule that comprises a vector operatively linked to a

nucleic acid segment defining a gene that encodes a recombinant HBc protein molecule according to claim 42, or a variant, analog or complement thereof, and a promoter suitable for driving the expression of the gene in a compatible host organism.

104. A host cell transformed with a recombinant nucleic acid molecule according to claim 101.

105. The transformed host cell according to claim 104 wherein said host cell is selected from the group consisting of CHO, VERO or COS cells, *E. coli*, *S. cerevisiae*, *Pichia pastoris typhi*, *S. typhimurium* and a *S. typhimurium-E. coli* hybrid.

106. A host cell transformed with a recombinant nucleic acid molecule according to claim 102.

107. The transformed host cell according to claim 106 wherein said host cell is selected from the group consisting of CHO, VERO or COS cells, *E. coli*, *S. cerevisiae*, *Pichia pastoris typhi*, *S. typhimurium* and a *S. typhimurium-E. coli* hybrid.

108. A host cell transformed with a recombinant nucleic acid molecule according to claim 102.

109. The transformed host cell according to claim 108 wherein said host cell is selected from the group consisting of CHO, VERO or COS cells, *E.*

*coli*, *S. cerevisiae*, *Pichia pastoris typhi*, *S. typhimurium* and a *S. typhimurium-E. coli* hybrid.

110. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine or inoculum according to claim 79, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.

111. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine or inoculum according to claim 80, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.

112. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine or inoculum according to claim 82, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.

113. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine or inoculum according to claim 87, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.

114. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine

or inoculum according to claim 88, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.

115. A method of inducing an immune response in an inoculated host animal that comprises the steps of inoculating a host animal with a vaccine or inoculum according to claim 92, and maintaining that inoculated animal for a time period sufficient for that animal to develop an immune response.